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Research Article

Congenital Malaria in Sudan

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Abstract

Malaria infection in the neonate may be defined as congenital if it occurs within the first 7 days of life. This timing is based on the knowledge that transplacental transfer of malarial immunity from mother to fetus occurs during the latter half of pregnancy, such that the newborn generally has a higher risk of infection as transplacentally acquired immunity wanes. Although this definition distinguishes congenital malaria from other neonatal infections, it is an arbitrary distinction in terms of the infant's clinical presentation. Several studies on congenital malaria include infants up to 28 days of age, which is the standard definition of the neonatal period. In these studies, infants with fever and parasitemia were considered to have neonatal malaria, and if there was documented involvement of only the transplacental route of infection it was termed congenital malaria. The two groups have been included together in some discussions of neonatal malaria, and even in areas of intense transmission, distinguishing between in utero and postnatal infection can be difficult because of the short interval between these two periods. For example, infants in hyperendemic areas may have parasitemia due to transmission during or immediately after delivery, or through inoculation during the early neonatal period. Simulation models of malaria transmission have suggested that transplacental infection is relatively frequent and may be an important factor in the spread of malaria, but such infections are a difficult and often impossible endpoint to distinguish from those resulting from early postnatal transmission.

Nevertheless, these issues should not diminish the significance of distinguishing between congenital malaria and other forms of neonatal infection. This classification recognises the unique mechanism of transplacental transmission, it underscores the special vulnerability of infants due to the lack of acquired immunity, and it has potentially important implications for the prevention and treatment of neonatal parasitemia. Congenital and in utero malaria are also topics of great interest in studies of fetal and early childhood development, given the many adverse effects that malaria may have on these processes. In this review, we will attempt to consider the full range of neonatal parasitemia in relation to fetal and early childhood outcomes, but a primary focus will be on congenital malaria at the onset of life outside the uterus.

1.Introduction

The prevalence and impact of CM are poorly understood. The incidence is underestimated because of diagnostic difficulties and asymptomatic parasitemia. Low birth weight, anemia, and perinatal mortality are believed by most fieldworkers to be increased by CM, but the clinical evidence is limited. A malarial etiology is often assumed, without supporting evidence from microscopy or other specific tests for malaria. The effects of CM on childhood morbidity and scholastic levels need clearer definition. A case definition of CM has recently been proposed to assist clinical diagnosis and research: asexual forms of P. falciparum on a blood film, with no evidence of a concomitant infection which might cause coma, in a deeply ill child from a malarious area. But the validity and reliability of this definition are uncertain, and will require research in areas with varying malaria endemicity.

To date, most field studies of CM have been small and cross-sectional, often with non- parasitemic controls. Results are conflicting between different studies and different settings. Longitudinal studies of clinical epidemiology have been rare. Few studies have used standardized methods to define exposure to malaria, or to define the pathology of the presenting encephalopathy. Management of cases has been highly variable. Most children in Africa with convulsions or coma are not seen in hospital, and coma in a malarious area may have many causes, so that the "CT scan and lumbar puncture" model of research into pediatric encephalopathy will not be feasible in most malarious areas for some time. Subtle neurological sequelae of CM are poorly understood because of a lack of follow-up studies. Treatment and prevention strategies have been based on poor quality evidence.

2. Prevalence of Congenital Malaria

In recent years, studies of congenital malaria have been conducted in several countries in Africa, our own being in western Sudan. Despite the availability of medication and treatment for malaria, the number of affected individuals continues to grow. In our attempt to determine the prevalence of congenital malaria in children born to mothers with malaria, we conducted surveys in different areas of the country. A total of 877 children were examined consisting of 637 from an area with unstable malaria and 240 from an area of stable malaria. This variation was an attempt to see if the rate of congenital malaria differed in areas where malaria itself is of varying prevalence.

Out of the 877 children examined, 71 tested positive for malaria displaying a prevalence of ~8%. This number alone gives us good reason to observe the situation more closely, however the prevalence for those children born in the area of unstable malaria was ~12% compared to only ~2% for those in the stable area. At the time

of delivery, blood was taken from the mothers to examine whether antimalarial treatment during pregnancy would have any effect on the infant. The results showed that there was no significant difference in the rate of congenital malaria between treated and untreated mothers. It was a common belief that antimalarial therapy during pregnancy resulted in a lower risk of congenital malaria in the infant but current results indicate otherwise. However, these results must be taken with caution due to the small size of the study group and lack of monitoring for compliance in taking the medication.

3.Risk Factors for Congenital Malaria

Women living in endemic areas are susceptible to malaria attacks when attending antenatal clinics, which usually occur later in pregnancy and thus have been associated with higher transmission and increased susceptibility of the fetus to the parasite Pregnant women decrease expression of Th1- type cytokines that are important in controlling parasite multiplication in order to avoid fetal rejection In endemic areas, the first or second pregnancy is statistically more likely to have adverse effects because the woman has not yet acquired immunity to placental sequestration of P. falciparum infected erythrocytes, a variant-specific process, and thus is susceptible to the parasite's ability to adhere and accumulate in the placenta by binding to receptors including chondroitin sulphate A, ICAM-1, and CD36.

This sequestration causes inflammation and placental damage and can result in maternal anemia and low birth weight of the infant [32]. Immunity to placental malaria is polymorphic and acquired over successive pregnancies, with women in high endemic areas with parity of 5 or more less likely to contract malaria than during their first pregnancy [33]. Infant immunity is high during the first few months of life due to passively acquired maternal antibodies, although these antibodies are short-lived and the infant becomes susceptible to clinical malaria during the first year of life, it is imperative that the mothers and infants take precautionary measures to prevent infection and disease.

4.Diagnosis and Treatment of Congenital Malaria

Identification of the infecting Plasmodium species by blood film examination is important because antimalarial treatment for congenital malaria can differ based on the infecting species. Polymerase chain reaction (PCR) can have a role in diagnosis, but at present it is not a practical tool in the periphery where most neonates with congenital malaria are seen, particularly in sub-Saharan Africa. As many as 50% of neonates of febrile mothers with acute malaria in sub-Saharan Africa may have parasites in their peripheral blood but have no clinical symptoms of malaria. Such neonates have "asymptomatic parasitemia".

Randomized controlled trials of treatment of asymptomatic parasitemia or prevention of adverse clinical events in this population of neonates have not been conducted, and a strategy for managing these neonates has not been defined. If the mother or newborn receives a clinical intervention in a trial related to the child's malaria infection (e.g. treatment of antenatal anemia or prevention of low birth weight), the child's malaria infection often is not monitored, although it may be one of the important clinical outcomes.

Malaria infection is often difficult to diagnose in neonates because their clinical symptoms of fever, vomiting, poor feeding, anemia, or jaundice can be caused by many different neonatal infections. Diagnosis in the neonate should always be followed by prompt treatment. Microscopic examination of thin and thick blood films remains the "gold standard" for laboratory diagnosis of malaria. Blood films should be repeated every 6-12 hours in neonates with suspected congenital malaria because parasitemia can be cyclic, and absent or low parasitemia in the peripheral blood may not exclude severe or complicated disease.

Treatment options and challenges

ACTs should be taken for 3 days, and a single dose of primaquine should be administered after excluding glucose-6-phosphate dehydrogenase-deficient mothers, who may cause hemolysis in the newborn. Treatment for convulsion should be further investigated, as different drugs are foreseen as second-line anticonvulsant therapy. Derived from the described complexities in treating neonates, the Sudan control program, including the guideline drafters, is encouraged to revisit the current policy in supporting congenital malaria. Based on WHO recommendations, amodiaquine should be the drug of choice for treating congenital malaria, replacing the currently used ACT regimen. Amodiaquine is known to be well tolerated and has proven to be safe even in the first year of life. It also has logistic advantages against AS or IV for rectal use.

Currently, artemisinin-based combination therapy (ACT) is the treatment of choice for malaria. Consistent with findings in congenital malaria studies and guidelines for neonatal malaria management, Artesunate (AS) is given as rectal treatment at primary health care facilities in all suspected severe malaria cases and in all protracted febrile illness patients. Intravenous artesunate (IV AS) is recommended for the treatment of severe falciparum malaria cases that fulfill certain criteria. However, the risk of overdosing of artesunate by weight as well as safety concerns in small infants is critical in congenital malaria management.

All clinical trials are conducted in neonatal period use IM artmether or Quinin IM / IV Which widely used method.

5. Prevention and Control Measures

Once a case of malarial infection is detected in a pregnant woman, prompt and effective case management is called for. This would include adequate treatment for the mother, to prevent the infection progressing to a stage where it becomes potentially fatal or severe enough to result in placental transmission, as effective treatment of just the symptomatic infection could significantly increase the level of naturally acquired immunity. It is difficult for many women to avoid exposure to infective mosquito bites, therefore it is important for chemoprophylaxis to be available for those living in high-risk areas.

Unfortunately, as there are safety concerns regarding the use of many antimalarial drugs in the first trimester or throughout pregnancy, having the necessary drugs that can be taken without risk to the unborn child is an area with little current progression.

An approach to control congenital malaria is to reduce the exposure of pregnant women to infective mosquito bites. Protection can be achieved by the use of personal measures (such as insecticide-impregnated bed nets, insecticide treated clothes and/or skin repellents) or environmental (such as mosquito-proof houses). In malaria endemic rural areas, bed nets have proven to be highly effective in preventing cases of severe malaria in young children and congenital transmission is likely to be reduced by their use in pregnant women. An entomological study from Malawi has confirmed that indoor residual spraying is effective in reducing the numbers of mosquitoes and preventing malaria transmission during the hours spent inside before going to bed. Due to the greater vulnerability of pregnant women, it would not be surprising for them to be willing to spend the additional money to effectively protect their families, particularly if the safety of the insecticides can be clearly demonstrated.

Conclusion

Improved treatment strategies for CM in neonates are much needed, since it remains a relatively neglected disease area. Drug treatment must fulfill several criteria including safety in early infancy, efficacy against the varied etiology and location of infection, ease of administration and low cost. Development of new drugs which fulfill these criteria is also much needed in the global context of malaria control, where increasing resistance and unsatisfactory efficacy of currently available drugs are a major concern. CM is an important determinant of neonatal mortality, yet very few studies have evaluated the specific treatment requirements for neonatal CM. Most trials of antimalarial drugs have been conducted in older children and adults, and treatment regimens are largely extrapolated from these trials. Both the pharmacokinetic properties of antimalarial drugs

in neonates and the optimum dosage and duration of treatment for severe malaria in this age group are essentially unknown.

This is an area where clinical studies in neonates with and without CM, using a combination of pharmacokinetic, pharmacodynamic and clinical endpoints, could greatly improve the evidence base for treatment of neonatal malaria.

The comparative safety and efficacy of the different Artemisinin combination therapies (ACTs) in treatment of CM in African children is the subject of an extensive program of clinical trials and pharmacovigilance. This development is of immediate relevance to treatment of CM in the neonatal population in regions where ACTs are now being deployed to replace failing first line drugs. Yet again, there is almost no data on the use of ACTs in newborn infants. Key issues in evaluating the problem of CM treatment in neonates include consideration of the poor access to health care for this vulnerable population in malaria endemic countries, and the fact that the majority of sick neonates will never reach a hospital where they can access high level medical care. This represents a further justification for research to improve currently available and feasible treatments such as antimalarial drugs given in the community, and to inform the optimal use of limited health resources to prevent adverse outcomes in this high risk group.